Cross-Talk Between Constitutive and Inducible Nitric Oxide Synthases

To the Editor,

We read with great interest the recent work by Kanno et al describing the protective effect of nitric oxide (NO) against myocardial ischemia/reperfusion injury and were struck by the other phenomenon associated with it: superinduction of inducible NO synthase (iNOS) in endothelial NO synthase (eNOS) knockout mice. Although the exact mechanism is unknown and apparently “paradoxical,” the absence of constitutive NO seems to increase inducible NO production. In this respect, the authors argued that the effect could be due to redox stress associated with the absence of NO.

Recently, we published an article suggesting cross-talk between constitutive and inducible NO synthase (NOS) using NO as a modulator. In particular, low (ie, physiological) NO levels inhibit iNOS transcription by inactivating nuclear factor-κB (NF-κB). However, when NO levels decrease beneath a putative threshold value (eg, as in eNOS knockout cardiomyocytes), they may not be sufficient to keep NF-κB suppressed, thus creating the favorable conditions for superinduction of NOS-II expression. Interestingly, the adaptive mechanism that the authors propose may simply reflect an acquired activation of NF-κB due to the absence of NO, leading to the change in redox stress.

Therefore, the work by Kanno et al introduces, for the first time, an ex vivo model indicating that intracellular amounts of NO may play a key role in modulating iNOS expression, thus providing further evidence for our hypothesis. However, other ex vivo or in vivo models should be examined to obtain more insight regarding the strict cross-talk between NO and NOS synthases.

Moreover, on the basis of evidence suggesting a beneficial effect of iNOS-produced NO, very low amounts of NO, which could potentially be harmful to the body by facilitating the induction of iNOS expression, may not (for the same reason) always be detrimental. The work by Kanno et al pointed out the importance of the physiologically present NO in downregulating the induction of iNOS. Attention should be paid to any trial that modulates intracellular amounts of NO. Any compound down-modulating the catalytic activity of constitutive NOS, such as specific inhibitors of constitutive NOS or NO donors that moderately increase intracellular NO levels, may exert more profound effects on the induction of iNOS expression than normally expected.

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Response

We are grateful to Dr Marco Colasanti and Prof Hisanori Suzuki for their comments and are pleased that they found our article of interest. They suggest a possible mechanism relating to our finding of superinduction of inducible nitric oxide synthase (iNOS) in the isolated hearts from endothelial NOS (eNOS) knockout mice subjected to warm ischemia reperfusion.

Recently Dr Marco Colasanti and Prof Hisanori Suzuki published a review in *Trends in Pharmacological Sciences* that presents a plausible mechanism for the superinduction of iNOS observed in our experiment. According to their review and previous work, this paradoxical induction of iNOS can possibly be explained by the following hypothesis. Low concentrations of NO, maintained by the activity of constitutive NOS, suppress the activation of nuclear factor-kB (NF-kB) under resting conditions. Therefore, it is reasonable to speculate that conditions that lead to a reduction in NO availability, such as suppressed or absent eNOS activity or removal of NO by other molecules (eg, oxygen radicals and heme-containing proteins), will facilitate NF-kB activation. Because NF-kB is one of the transcription factors required for the activation of the NOS gene, this could contribute to the hyperinduction of iNOS. However, it is unlikely that this hypothesis alone explains the hyperinduction of iNOS. For instance, it does not explain the triggering mechanism for the activation of NF-kB and iNOS expression. This is most likely due to the increased production of oxygen radicals. Because NO can neutralize oxygen radicals, it is also possible that basal levels of NO have an antioxidant function and that the increased oxidative stress resulting from the absence of constitutive levels of NO contributes to the hyperinduction of iNOS at reperfusion. There is ample evidence that supplementation with low levels of NO donors or providing arginine can be protective in models of ischemia-reperfusion.

Finally, we thank Dr Marco Colasanti and Prof Hisanori Suzuki for kindly suggesting a possible mechanism of superinduction of iNOS observed in eNOS knockout mice.

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